REMARKS/ARGUMENTS

With this amendment, claims 1, 5-9, and 14 are pending. New claim 14 is added. For convenience, the Examiner's rejections are addressed in the order presented in a September 8, 2004 Office Action.

I. Status of the claims

Step (a) of claim 1 is amended to recite that plasma is adjusted to a specified pH and conductivity to obtain a diluted plasma. Step (b) of claim 1 is amended to recite that the diluted plasma is contacted with an anion exchange resin. Support for these amendments is found at page 6 lines 24- 27 and at page 7, lines 8-10. These amendments are not limiting amendments and do not add new matter.

Step (a) of claim 1 is also amended to recite that plasma is adjusted to a pH of 6.5. Support for this amendment is found at page 6 lines 24- 27. This amendment adds no new matter.

New claim 14 is added and recites that the "cation exchange effluent consists essentially of IgG4." This amendment adds no new matter.

II. Rejections under 35 U.S.C. §103(a)

A. Introduction

Claims 1 and 5-9 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Laursen *et al.* (U.S. Patent No. 6,281,336) in view of Flaa *et al.* (U.S. Patent 6,165,336). In response, Applicants respectfully traverse the rejection. According to the Office Action, Laursen *et al.* teach production of purified IgG4. See, *e.g.*, Office Action at page 3, second paragraph and page 4, first paragraph. As explained below, this interpretation is not correct.

In order to establish a *prima facie* case of obviousness the Office Action must demonstrate that the cited references provide a suggestion or motivation for their modification or combination, a reasonable expectation of success in the combination, and that the references teach or suggest all the claim limitations. All three elements set forth above must be present in

order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations. As described below, Applicants assert that the citation of Laursen *et al.* and Flaa *et al.* fails to meet the standard for a prima facie case of obviousness. Neither of the cited references provide the required clear and particular evidence of a suggestion, teaching, or motivation for their combination. In addition, the cited references, alone or in combination, fail to provide all the elements of the claimed invention, *i.e.*, the combination of references fails to teach adjustment of plasma pH to ph 6.5 and similarly fails to teach manufacture of IgG4 that is essentially free of other IgG subtypes.

B. The cited art does not teach or suggest all the elements of the claimed invention.

The cited art fails to teach all the steps of the claimed methods, either alone or in combination. Laursen *et al.* teaches use of different method steps then the steps recited in the claims. Laursen *et al.* also arrive a different end product then the purified IgG4 recited in the claims. Flaa *et al* is silent as to stabilization of immunoglobulin proteins.

1. The cited art does not disclose adjustment of plasma pH to pH 6.5 as claimed.

Laursen *et al.* disclose a method of purifying total IgG from plasma that includes a step of adjusting the pH of plasma to a pH lower than 6.0, *e.g.*, preferable pH 5.4. See, *e.g.*, Laursen *et al.*, at column 5, lines 12-17. A pH below 6.0 is required to enhance a subsequent PEG precipitation step that is critical for removal of virus particles.

In contrast, the claimed invention is a method of manufacturing purified *IgG4 immunoglobulin subtype*, free of IgG1, IgG2 and IgG3 subtypes for the treatment of allergic reactions, including serious insect sting allergies. As a first step, the pH of plasma is adjusted to a value of 6.5, *i.e.*, a pH value greater than pH 6.0 as taught by the cited references. Clearly, a pH of 6.5 is greater than the maximum pH 6.0 allowed by Laursen *et al.*, and thus the method of Laursen is not encompassed by the claims.

Laursen *et al.* also teach away from use of pH values greater than 6.0, as used in the claimed methods. Laursen *et al.* state that a pH below 6.0 is required to solubilize the total IgG proteins, while precipitating harmful virus particles in a subsequent PEG precipitation step. Therefore, Laursen *et al.* teach away from use of pH values greater than 6.0, *e.g.* the claimed 6.5 pH value. Lacking the claimed adjustment of plasma pH to a value of 6.5, Laursen *et al.* fail to teach all the steps of the claimed method.

Flaa *et al.* teaches nothing regarding adjustment of plasma pH for purification of specific IgG subtypes and thus, even if combined with Laursen *et al.* does not remedy the deficiencies of that reference.

2. The cited art does not teach separation of IgG4 product from other IgG subtypes.

The amended claims are directed to manufacture of an IgG4 preparation that is essentially free of other IgG subtypes. In addition, new claim 14 is directed to a final product that consists essentially of IgG4. The cited art references, even if combined, teach only production of a preparation of a total IgG preparation, *i.e.* a preparation that includes IgG1, IgG2, IgG3, and IgG4. As described in detail below, applicants assert that the claimed methods separate IgG4 from other IgG subtypes found in the plasma starting material, as is required by the claims.

The Office Action, at page 3, second paragraph and page 4, first paragraph, alleges that the Laursen *et al.* teach production of purified IgG4. The Office relies on a Table in Laursen *et al* at columns 17 and 18 and on a description of an immundiffusion technique at column 20, lines 6-8. Applicants assert that this interpretation of Laursen *et al* is incorrect. Laursen *et al.* teach only a method of purifying total IgG from plasma and do not teach a method of purifying any IgG subtype, such as IgG4, away from a total IgG fraction to produce *i.e.*, IgG4 that is essentially free of other IgG subtypes as is claimed. Applicants provide evidence in the form of a declaration from inventor Dr. William Pollack that the total IgG fraction of Laursen *et al.* including that described in the Table at columns 17 and 18, is not a purified IgG that is

essentially free of other IgG subtypes. The declaration also provide evidence that the methods of Laursen *et al.* do not separate IgG4 from the other IgG subtypes of the total IgG fraction.

The Office Action also appears to assert that description of the quantitation IgG subclasses within the total IgG fraction in some way separates an IgG4 fraction from the other IgG subtypes within Laursen's total IgG product. The IgG subclass distribution reported in the reference was determined using immunodiffusion assays (see, *e.g.*, Laursen *et al.* at column 20, lines 6-8). Applicants present evidence from inventor Dr. William Pollack that IgG4 detected using a Mancini immunodiffusion assays is not an IgG4 preparation that is essentially free of other IgG subtypes. The total IgG sample was used in the diction assay and individual IgG subtypes were not fractionated before or during the assay. IgG4 specific antibodies were used to detect IgG4 and appropriate specific antibodies were used to detect other IgG subtypes in the total IgG preparation. Thus, even if characterization of IgG subtypes by immunodiffusion could somehow be construed to be a purification step, the IgG4 detected in the immunodiffusion assay is bound to specific antibodies and is not essentially free of other IgG subtypes as maintained by the Office Action.

Because neither the product of Laursen *et al.*, nor the product of the immunodiffusion assay are IgG4 that is essentially free of other IgG subtypes, Laursen *et al.* does not teach or disclose the methods to separate IgG4 from other IgG subtype and produce an IgG4 product that is essentially free of other IgG subtypes. The citation of Flaa *et al.* fails to remedy this deficiency of Laursen *et al.*

C. The cited art does not provide one of skill with a suggestion for modification or combination to arrive at the claimed invention.

Neither Laursen *et al.* nor Flaa *et al.* provide a clear and particular suggestion for their modification or combination to arrive at the claimed invention. First, Laursen *et al.* do not provide any suggestion or teaching of use of a purified IgG4 subtype, or any purified IgG subtype as a therapeutic. Laursen *et al.* teach only the therapeutic use of a virus-free, total IgG4 composition with subtype distribution close to that of human blood, *i.e.*, 1-3% IgG4. Second, Laursen *et al.* teach only treatment of disease or conditions that benefit from replacement or

supplementation of the total IgG component of blood, and for that purpose Laursen *et al.* explicitly require a total IgG preparation with subtype distribution close to that of human blood, *i.e.*, 1-3% IgG4 and 99-97% other IgG subtypes for that use. See, *e.g.*, Laursen *et al.* at column 20, lines 9-15. Flaa *et al.* teach only solutions for stabilizing purified proteins and do not teach any methods for purifying proteins, including immunoglobulins. Thus, neither Laursen *et al.* nor Flaa *et al.* provide the clear and particular suggestion or motivation for their modification or combination to arrive at the claimed invention.

In addition, Applicants respectfully remind the Examiner that there cannot be an adequate suggestion or motivation to make a proposed modification where such modification renders the prior art unsuitable for its intended purpose. *In re Gordon*, 221 USPQ 1125 (Fed. Cir. 1984); MPEP §2143.02. As Flaa *et al.* is cited only to provide teaching of addition of lactose, these remarks necessarily focus on the intended purpose of the total IgG preparations of Laursen *et al.* The Office Action's suggested modification of Laursen *et al.* to arrive at a purified IgG4 subtype to be "combined" with Flaa *et al.* would render the product unsuited to the use intended by Laursen *et al.*

Laursen *et al.* discloses a method of purifying a total IgG preparation from other plasma proteins with the intention of using the total IgG preparation to treat patients with diseases or conditions that benefit from replacement or supplementation of the total IgG component of blood. The Office Action appears to assume that one of skill would modify Laursen *et al.* by adjusting the pH to pH 6.5, thereby producing an IgG4 preparation. However, Laursen *et al.* specifically disclaim adjustment of plasma to pH values greater than 6.0 and the claimed pH 6.5 is greater than pH 6.0. Moreover, even if the teachings of Laursen *et al.* could be modified to arrive at a purified IgG4 preparation, as suggested by the Office Action, Applicants submit evidence in the form of a declaration from Dr. William Pollack that a purified IgG4 preparation would not be useful to treat diseases or conditions that benefit from replacement or supplementation of the total IgG component of blood as is intended by Laursen *et al.*

Laursen *et al.* also disclose that plasma pH values below pH 6.0 are critical to "ensure optimal effect of the subsequent PEG precipitation step." Laursen *et al.* at column 5, lines 16-17. The PEG precipitation step is disclosed as to critical to the methods of Laursen *et*

al. because it stabilizes the total IgG products and because it functions as a virus removal step. Laursen *et al.* at column 6, lines 2-6. As Laursen *et al.* prepare their total IgG preparation for safe intravenous administration, Applicants submit evidence in the form of a declaration from Dr. William Pollack that modifications, such as increasing the pH of plasma proteins, that interfere with virus removal by PEG precipitation, will render the product unsuitable for its intended use as a safe therapeutic for treatment of diseases or conditions that benefit from replacement or supplementation of the total IgG component of blood.

Thus, the combination or modification of the method of Laursen *et al.* and Flaa *et al.* to result in production of an IgG4 preparation that is essentially free of other IgG subtypes, in fact cannot be used as intended by the references, and cannot provide a motivation or suggestion for their modification or combination.

In summary, the references cited by the Office Action fail to provide all the steps of the claimed methods, *e.g.*, adjustment of plasma pH to pH 6.5 and separation of IgG4 from other IgG subtypes, to obtain a cation exchange effluent that comprises IgG4 essentially free of other IgG subtypes. The references also fail to provide a clear and particular suggestion or motivation for their combination or modification to arrive at the claimed invention. Finally, the modification of the Laursen *et al.* reference to arrive at an IgG4 preparation that is essentially free of other IgG subtypes would render the reference unusable for its intended purpose, and therefore unable to provide motivation for its modification. In view of the above amendments and remarks, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

II. Rejections under 35 U.S.C. §112, second paragraph

Claims 1 and 5-9 are rejected under 35 U.S.C. §112, second paragraph for allegedly failing to particularly point out and distinctly claim the subject matter regarded by the Applicant as the invention. The Examiner objects to use of the word about to qualify a pH value in claim 1. Without conceding to the propriety of the rejection and n order to expedite prosecution, claim 1 is amended to recite "pH 6.5" instead of "about pH 6.5."

Claims 1 and dependent claims 5-9 are also rejected for use of the phrase "obtained from" in step (b) of claim 1. In order to expedite prosecution, step (a) of claim 1 is amended to recite that plasma is adjusted to a specified pH and conductivity to obtain a "diluted plasma." Step (b) of claim 1 is amended to recite that the "diluted plasma of step (a)" (rather than "obtained from") is contacted with an anion exchange resin.

In view of the above amendments and remarks, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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